the art would appreciate that a DNA molecule which is prepared for transfection into a cell as described in Hodgson has been completely ligated; thus Hodgson describes adding the compacting agents after ligation has taken place. Hodgson's description of adding compacting agents to transfectable constructs distinguishes this document from the rejected claims, which specifically describe the addition of compacting agents **prior** to the ligation reaction.

As further proof against the anticipation of the rejected claims by Hodgson et al., the Applicant has noted that Hodgson does not disclose a concentration of compacting agent which allows enough flexibility for the linear DNA to form circular constructs. However, the Office Action states that consideration of the increased rigidity of condensed DNA is not necessary when applying the methods of Hodgson et al. to the rejected claims.

In support of this position, the Office Action asserts that the rigidity of condensed DNA was not well known in the art at the time this application was filed. Contrary to this assertion, textbooks from the relevant time period indicate that histones, especially in the presence of H1, can create extremely dense superstructure. Indeed, the textbooks show that DNA is not only wrapped around histones in linear nucleosomic array, but the nucleosome units are also further coiled and packed into a 30 nm diameter fiber chromatin or even denser heterochromatin. A representative textbook is Lewin B, Genes VI, Oxford Univ. Press, Inc., New York (1997), p769 (copy attached), which states:

> The nucleosome contains ~200 bp of DNA, organized by an octamer of small, basic proteins into a bead-like structure. The protein components are histones. They form the interior core; the DNA lies on the surface of the particle. Nucleosomes are an invariant component of euchromatin and heterochromatin in the interphase nucleus, and of mitotic chromosomes. The formation of the nucleosome forms the first level of organization, giving a packing ratio of ~6.
>
> The second level of organization is the coiling of the series of nucleosomes into a helical array to constitute the ~30 nm fiber that is found in both interphase chromatin and mitotic chromosomes.

The Applicant and Examiner agree that, although linear DNA condensed in this manner is most likely not rigid in an absolute sense, the flexibility of the DNA is reduced to some degree. This reduced flexibility is sufficient to cause the two extremities of a linear molecule to have difficulty contacting each other and forming a complete circular construct. Indeed, an

excess of histones inhibits the synthesis of a functional construct due to either reduced flexibility or an interaction between the histones and ligase enzymes.

The Office Action further asserts that, although flexibility may be reduced when DNA is condensed, the Hodgson process used an amount of compacting agent which prevented rigidity because it yielded successful ligation. However, the results achieved by Hodgson do not indicate that the concentration of compacting agent described therein was sufficient to allow the flexibility required for an active ligation reaction. Since Hodgson describes addition of the compacting agents to the medium after the circular constructs are already complete, it is impossible to determine if the concentrations of DNA compaction agent disclosed in Hodgson would have permitted completion of the actual ligation reaction. Thus, Hodgson does not disclose concentrations of condensing agents sufficient to allow either flexibility or ligation, as recited in the rejected claims.

Hodgson also does not inherently disclose every element of the rejected claims. For a claim element to be inherently disclosed in a prior art reference, that element must inevitably result from the teaching of the reference. As discussed above, one skilled in the art cannot determine from the teachings of Hodgson whether the disclosed concentrations of DNA compaction agent would or would not result in a successful ligation reaction. Thus, Hodgson does not disclose a concentration of compacting agent which inevitably allows enough flexibility for the linear DNA to form circular constructs.

Because Hodgson does not disclose, either expressly or inherently, every element of claims 11-14, 16-18, 22, 23, and 28, the anticipation rejection of these claims should be withdrawn.

Claim Rejections- 35 U.S.C. §103(a)

Claims 20 and 21 stand rejected under U.S.C. 103(a) as being unpatentable over Hodgson in view of Nagaki. The Office Action admits that Hodgson fails to disclose the claimed concentration of compacting agent, but that Nagaki allegedly cures this deficiency and renders claims 20 and 21 obvious. The Applicant maintains, however, that the concentration of HMG protein disclosed in Nagaki publication does not teach or suggest a concentration of compacting agent which inevitably allows enough flexibility for the linear DNA to form circular constructs,

and thus this document does not cure the deficiencies of Hodgson. The theoretical combination of Hodgson and Nagaki therefore does not render claims 20 and 21 obvious.

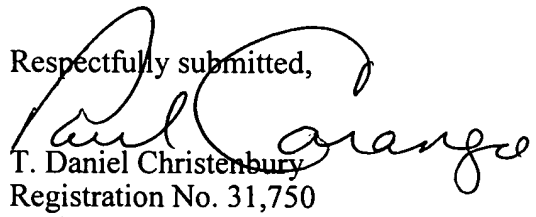
Claims 20 and 21 are directed to a process of creating circular recombinant nucleic acids. Nagaki discloses a process of making linearized dimers. As discussed in the Applicant's specification, compacting agents are required to reduce the distance between the termini of large linear nucleic acids and facilitate ligation into circular molecules. However, the use of HMG proteins as taught by Nagaki does not lead to circularized dimers, and are merely depicted as auxiliary proteins of ligation and the cellular process of recombination. This interpretation is supported by the fact that only linearized dimers are formed by the method taught by Nagaki. The fact that the HMG proteins as used by Nagaki do not aid in circularization of nucleic acids distinguishes them from DNA compacting agents as recited in claims 20 and 21. Since the HMG proteins as discussed in Nagaki play a distinctly different role than the claimed compacting agents, any concentrations or experimental methods disclosed in Nagaki are irrelevant to the method as recited in claims 20 and 21.

The teachings of Hodgson are discussed above. The theoretical combination of Hodgson and Nagaki would not suggest the method of claims 20 and 21 to one of ordinary skill in the art, nor would they provide a reasonable expectation that the claimed method could be successfully practiced. The rejection of claims 20 and 21 under 35 USC 103 (a) over Hodgson in view of Nagaki should therefore be withdrawn.

Conclusion

Based on the foregoing, the Applicant believes that the present application is in a condition for allowance. Favorable reconsideration of the claims is requested.

Respectfully submitted,



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